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IN THE SPECIFICATION

Cross-Reference to Related Applications

This application claims the benefit of U.S. Provisional Patent Application Serial No. 60/246,870, filed November 8, 2000.

Field of the Invention

The present invention relates to the field of ophthalmic solutions and their uses. In particular the invention relates to contact lens cleaning solutions, contact lens rinsing and storing solutions, solutions to deliver active pharmaceutical agents to the eye, solutions for disinfecting ophtalmic devices and the like.

Background

The present invention relates to the field of ophthalmic solutions and especially to the aspects of preservative efficacy and comfort after prolonged use. These ophthalmic solutions have been used for some period of time and are available as over the counter products. Solutions that are used in direct contact with corneal tissue such as the delivery of active pharmaceutical agent to the eye, or indirectly, such as the cleaning, conditioning or storage of devices that will come in contact with corneal tissue, such as contact lenses, there is a need to insure that these solution do not introduce sources of bacterial or other microbial infection. Thus preservatives are included to reduce the viability of microbes in the solution and to lessen the chance of contamination of the solution by the user since many of the solutions are bought, opened, used, sealed and then reused.

State of the art preservative agents include polyhexamethylene biguanide (PHMB), Polyquad ^{tm}, chlorhexidine, and benzalkonium chloride, and the like, all of which at some concentration irritate corneal tissue and lead to user discomfort. Therefore, a solution that employs a given amount of a preservative agent, but which is made

more effective by addition of an agent that is not a preservative agent would be desired.

Summary of the Invention

The present invention relates to improved ophthalmic solutions that employ inositol in order to more effectively preserve solutions and to reduce the degree to which cationic preservatives will deposit on contact lenses. Ophthalmic solutions are here understood to include contact lens treatment solutions, such as cleaners, soaking solutions, conditioning solutions and lens storage solutions, as well as wetting solutions and in-eye solutions for treatment of eye conditions.

The solutions specifically described herein have 0.001 to about 1 percent of simple saccharides in combination with other active ingredients useful in ophthalmic solutions such as buffers, preservatives, surfactants, and antimicrobial agents, and with a low chloride concentration, less than about 0.2 percent by weight. It has been found, surprisingly that inositol, and other sugars including mannitol, sorbitol, sucrose, dextrose, glycerin and propylene glycol, effectively increase the antibacterial effect of preservatives in low salt (low chloride) conditions.

The preservatives that are specifically useful are cationic polymeric preservatives such as polyhexamethylene biguanide (PHMB), Polyquad tm, chlorhexidne, and benzalkonium chloride, as well as other cationic preservatives that may prove useful in the present invention as well. The cationic preservatives are used at effective amounts as preservatives, and in the instance of PHMB from 0.0001 percent by weight to higher levels of about 0.01 weight percent. Specifcally, The cationic polymeric preservative includes polymeric biguanides such as polymeric hexamethylene biguanides (PHMB), and combinations thereof. Such cationic polymeric biguanides, and water-soluble salts thereof, having the following formula:

$$X^1-\left[Z-NH-\underset{\underset{NH}{\|}}{C}-NH-\underset{\underset{NH}{\|}}{C}-NH\right]_n-Z-X^2$$

wherein Z is an organic divalent bridging group which may be the same or different throughout the polymer, n is on average at least 3, preferably on average 5 to 20, and X^1 and X^2 are

$$-NH_2 \quad \text{and} \quad -NH-\underset{\underset{NH}{\|}}{C}-NH-CN$$

One preferred group of water-soluble polymeric biguanides will have number average molecular weights of at least 1,000 and more preferably will have number average molecular weights from 1,000 to 50,000. Suitable water-soluble salts of the free bases include, but are not limited to hydrochloride, borate, acetate, gluconate, sulfonate, tartrate and citrate salts.

The above-disclosed biguanides and methods of preparation are described in the literature. For example, U.S. Pat. No. 3,428,576 describes the preparation of polymeric biguanides from a diamine and salts thereof and a diamine salt of dicyanimide.

Most preferred are the polymeric hexamethylene biguanides, commercially available, for example, as the hydrochloride salt from Avecia (Wilmington, Del.) under the trademark Cosmocil™ CQ. Such polymers and water-soluble salts are referred to as polyhexamethylene (PHMB) or polyaminopropyl biguanide (PAPB). The term polyhexamethylene biguanide, as used herein, is meant to encompass one or more biguanides have the following formula:

$$X^1 - [Z - NH - \underset{\underset{NH}{\|}}{C} - NH - \underset{\underset{NH}{\|}}{C} - NH]_n - Z - X^2$$

wherein Z, X^1 and X^2 are as defined above and n is from 1 to 500.

Depending on the manner in which the biguanides are prepared, the predominant compound falling within the above formula may have different X^1 and X^2 groups or the same groups, with lesser amounts of other compounds within the formula. Such compounds are known and are disclosed in U.S. Pat. No. 4,758,595 and British Patent 1,432,345, which patents are hereby incorporated. Preferably, the water-soluble salts are compounds where n has an average value of 2 to 15, most preferably 3 to 12.

It was found that an unexpected preservative efficacy was displayed when inositol was used in conjunction with the cationic preservative. The other components of the solution are used at levels known to those skilled in the art in order to improve the wearability of lenses and when used directly in the eye, to provide increased resistance to infection. Inositol used in ophthalmic solutions increases preservative efficacy in certain formulations, provides increased resistance to infection in corneal tissue, in certain formulations, and improves the quality of tears in certain formulations.

The formulations may also include buffers such as phosphates, bicarbonate, citrate, borate, ACES, BES, BICINE, BIS-Tris, BIS-Tris Propane, HEPES, HEPPS, imidazole, Tris, MES, MOPS, PIPES, TAPS, TES, Glycine and Tricine

Surfactants that might be employed include polysorbate surfactants, polyoxyethylene surfactants, phosphonates, saponins and polyethoxylated castor oils, but preerrably the polyethoxylated castor oils. These surfactants are commercially available. The polyethoxylated castor oils are sold by BASF under the trademark Cremaphor.

Inositol, mannitol, sorbitol, sucrose, dextrose, glycerin, propylene glycol and the other agents used in the present invention are all commercially available, and well enough understood to be formulated into products within the scope of the invention by those skilled in the art.

The solutions of the present invention may contain other additives including but not limited to buffers, tonicity agents, demulcents, wetting agents, preservatives, sequestering agents (chelating agents), surface active agents, and enzymes.

Other aspects include adding to the solution from 0.001 to 1 weight percent chelating agent (preferably disodium EDTA) and/or additional microbicide, (preferably 0.00001 to 0.1 or 0.0000 1 to 0.01) weight percent polyhexamethylene biquanide (PHMB, N-alkyl-2-pyrrolidone, chlorhexidine, polyquaternium- 1, hexetidine, bronopol, alexidine, low concentrations of hydrogen peroxide, and ophthalmologically acceptable salts thereof

Ophthalmologically acceptable chelating agents useful in the present invention include amino carboxylic acid compounds or water-soluble salts thereof, including ethylenediaminetetraacetic acid, nitrilotriacetic acid, diethylenetriamine pentaacetic acid, hydroxyethylethylenediaminetriacetic acid, 1,2-diaminocyclohexanetetraacetic acid, ethylene glycol bis (beta-aminoethyl ether) in N, N, N', N' tetraacetic acid (EGTA), aminodiacetic acid and hydroxyethylamino diacetic acid. These acids can be used in the form of their water soluble salts, particularly their alkali metal salts. Especially preferred chelating agents are the di-, tn- and tetra-sodium salts of ethylenediaminetetraacetic acid (EDTA), most preferably disodium EDTA (Disodium Edetate).

Other chelating agents such as citrates and polyphosphates can also be used in the present invention. The citrates which can be used in the present invention include citric acid and its mono-, di-, and tri-alkaline metal salts. The polyphosphates which can be used include pyrophosphates, triphosphates, tetraphosphates,

trimetaphosphates, tetrametaphosphates, as well as more highly condensed phosphates in the form of the neutral or acidic alkali metal salts such as the sodium and potassium salts as well as the ammonium salt.

The pH of the solutions should be adjusted to be compatible with the eye and the contact lens, such as between 6.0 to 8.0, preferably between 6.8 to 7.8 or between 7.0 to 7.6. Significant deviations from neutral (pH 7.3) will cause changes in the physical parameters (i.e. diameter) in some contact lenses. Low pH (pH less than *5.5)* can cause burning and stinging of the eyes, while very low or very high pH (less than 3.0 or greater than 10) can cause ocular damage.

The additional preservatives employed in the present invention are known, such as polyhexamethylene biguanide, N-alkyl-2-pyrrolidone, chlorhexidine, polyhexamethylenebiguanide, alexidine, polyquaternium- 1, hexetidine, bronopol and a very low concentration of hydrogen peroxide, e.g., 30 to 200 ppm.

The solutions of the invention are compatible with both rigid gas permeable and hydrophilic contact lenses during storage, cleaning, wetting, soaking, rinsing and disinfection.

A typical aqueous solution of the present invention may contain additional ingredients which would not affect the basic and novel characteristics of the active ingredients described earlier, such as tonicity agents, surfactants and viscosity inducing agents, which may aid in either the lens cleaning or in providing lubrication to the eye. Suitable tonicity agents include sodium chloride, potassium chloride, glycerol or mixtures thereof The tonicity of the solution is typically adjusted to approximately 240-310 milliosmoles per kilogram solution (mOsm/kg) to render the solution compatible with ocular tissue and with hydrophilic contact lenses. In one embodiment, the solution contains 0.01 to 0.2 weight percent sodium chloride. The important factor is to keep the concentrations of such additives to a degree no greater than that would supply a chloride concentration of no greater than about 0.2

mole percent.

Suitable viscosity inducing agents can include lecithin or the cellulose derivatives such as hydroxymethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose (HPMC), and methylcellulose in amounts similar to those for surfactants, above.

Example 1

An example of a formulation containing low salt, a buffer and cationic preservative follows:

Log Reduction	Buffer	Preservative	Preservative Enhancer	Wetting Agent
2.27	none	PHMB 0.0001%	None	None
3.85	Bis-Tris Propane 0.2%	PHMB 0.0001%	None	Cremophor ®RH 40
4.40	Bis-Tris Propane 0.2%	PHMB 0.0001%	propylene glycol 3%	Cremophor ®RH 40
4.40	Bis-Tris Propane 0.2%	PHMB 0.0001%	sorbitol 5%	Cremophor ®RH 40
4.40	Bis-Tris Propane 0.2%	PHMB 0.0001%	inositol 5%	Cremophor ®RH 40
2.98	Marketed Product 1			
0.68	Marketed Product 2			
2.99	Marketed Product 3			

Column 1 shows the reduction of *C. albicans* at 2 hours using a typical antibacterial test . The data shows improved activity over the preservative alone; improved activity over the buffer control without sugar additive and improved activity over commercially available products

Example 2

Log Reduction	Buffer	Preservative	Additive
2.53	none	PHMB 0.0001%	none
1.34	Bis-Tris Propane 0.2%	PHMB 0.0001%	sodium chloride 0.5%

3.42	Bis-Tris Propane 0.2%	PHMB 0.0001%	glycerin 0.5%
2.73	Bis-Tris Propane 0.2%	PHMB 0.0001%	propylene glycol 0.5%
1.13	Bis-Tris Propane 0.2%	PHMB 0.0001%	potassium chloride 0.5%
3.92	Bis-Tris Propane 0.2%	PHMB 0.0001%	sorbitol 0.5%
3.23	Bis-Tris Propane 0.2%	PHMB 0.0001%	mannitol 0.5%
3.06	Bis-Tris Propane 0.2%	PHMB 0.0001%	inositol 0.5%
3.72	Bis-Tris Propane 0.2%	PHMB 0.0001%	dextrose 0.5%

This data shows that the antimicrobial activity of buffer with the sugar or glycol is greater than the preservative alone and that decreased acitivity at 0.5% sodium chloride or 0.5% potassium chloride solutions occurs as well. Thus the surprising effect of the sugar derived preservative enhancers is displayed and the effects relationship to chloride concentration is demonstrated.

Example 3

Solutions with a cationic polymeric preservative (PHMB) sodium chloride and glycerin and a buffer were made as shown in the following table and the preservative efficacy was measured.

Log Reduction	Buffer	Preservative	Sodium Chloride	Glycerin
1.69	none	PHMB 0.0001%	none	none
1.74	none	PHMB 0.0001%	0.1%	none
1.46	none	PHMB 0.0001%	0.2%	none
0.86	none	PHMB 0.0001%	0.4%	none
0.49	none	PHMB 0.0001%	0.5%	none
2.44	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	none
1.89	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.1%	none
1.54	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.2%	none
0.98	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.4%	none
0.89	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.5%	none

2.46	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	0.20%
2.41	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	0.50%

The above date illustrates the effect of sodium chloride on preservative efficacy and the effect of glycerin in improving preservative efficacy in low salt solutions.

Example 4

Solutions were made according to methods described supra with sodium phosphate as the buffer.

Log Reduction	Buffer	Preservative	Tonicity Agent
0.79	Sodium Phosphate 0.2%	PHMB 0.0001%	none
0.33	Sodium Phosphate 0.2%	PHMB 0.0001%	Sodium Chloride 0.7%

This data illustrates the problem with sodium chloride is independent of buffer type.

Example 5

Solutions were formulated with sodium chloride, sorbitol and sucrose and then lenses were immersed in the resultant solutions and chlorohexidine gluconate was added. The lenses were exposed for 3 hours and the amount of the chlorohexidine deposited on the lens was measured.

Method:	HPLC analysis for chlorhexidine gluconate
	3.0 mL solution exposed to 1/2 lens
Matrix:	1 ppm CHG / 0.2% Bis-Tris Propane / 0.1% Cremophor RH 40
Lens:	Freshlook ColorBlends (45% phemfilcon A, 55% water) Wesley Jes:

Additive	ug CHG per lens	% Decrease
None	4.0	67.3%
Sodium Chloride	3.6	59.3%
Sorbitol	3.0	50.7%
Sucrose	1.3	21.4%

1 ppm CHG Std in water	%RSD through the entire experiment	2.9%

This test shows that the sugars used in the test have an ability to decrease the extent of preservative binding for of cationic preservatives when properly formulated. Both sorbitol and sucrose solutions demonstrated efficacy in reducing preservative deposition.

Example 6

The following experiment demonstrates the effect of chloride concentration on the antimicrobial effectiveness of PHMB preservative solutions.

Log Reduction	Buffer	Preservative	NaCl	Additive	Effect
1.05	Bis-Tris 0.2%	PHMB 0.0001%	none	none	54%
1.47	Bis-Tris 0.5%	PHMB 0.0001%	none	none	75%
0.77	Bis-Tris 0.2%	PHMB 0.0001%	0.70%	none	39%
2.39	Bis-Tris Propane 0.2%	PHMB 0.0001%	none	none	123%
2.32	Bis-Tris Propane 0.5%	PHMB 0.0001%	none	none	119%
0.91	Bis-Tris Propane 0.2%	PHMB 0.0001%	0.70%	none	47%
1.27	Tricine 0.2%	PHMB 0.0001%	none	none	65%
1.31	Tricine 0.5%	PHMB 0.0001%	none	none	67%
0.62	Tricine 0.2%	PHMB 0.0001%	0.70%	none	32%